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Template version 09/11

TXR#: 0056765

DATA EVALUATION RECORD[1]

STUDY TYPE: Subchronic Oral Toxicity, Dog; Capsule
OPPTS 870.3150 [§82-1b]; OECD 409.

PC CODE: 016331 **DP BARCODE:** D410187

TEST MATERIAL (PURITY): Momfluorothrin (95.7% a.i.)

SYNONYMS: S-1563

CITATION: Braun, L. (2011). 13-Week Repeated Dose Oral (Capsule) Toxicity Study in the Beagle Dog Followed by a 6-Week Recovery Period. Harlan Laboratories Ltd, Itingen, Switzerland. Harland Laboratories Study #C61698, December 9, 2011. MRID 49020008. Unpublished.

SPONSOR: Sumitomo Chemical Company, Ltd.

EXECUTIVE SUMMARY:

In a 90-day oral toxicity study (MRID 49020008), S-1563 (Momfluorothrin, 95.7% a.i./Batch #9CM0109G) was administered to Beagle dogs, 4/sex/dose, in capsules at dose levels of 0, 50, 200, or 600 mg/kg/day. In addition, 2/sex/dose in the control and high-dose groups were observed for a 6-week recovery period after 90 days of treatment.

Higher incidences of watery, mucus or discolored feces and vomiting of mucus or feed were recorded in both sexes of the 600 mg/kg/day group. These signs were absent in the 6-week recovery animals. No treatment-related effects were observed on mortality, body weights, ophthalmology, hematology, or macroscopic examination.

Slight evidence of hepatotoxicity (increased liver weights, increased cholesterol and triglyceride levels, and histopathological findings) was observed in both sexes at 600 mg/kg.

The systemic toxicity LOAEL for this study is 600 mg/kg/day based on clinical signs (watery, mucus or discolored feces and vomiting of mucus or feed) and slight evidence of hepatotoxicity including non-significant, but dose-related, increases in liver weights, and slight to minimal hepatocellular hypertrophy. The systemic toxicity NOAEL is 200 mg/kg/day.

1 Disclaimer: The attached Data Evaluation Record is a modified version of the Tier II Summary provided by Sumitomo Chemical Co. Ltd. Portions of this document may have been altered by the EPA reviewer.

This 90-day oral toxicity study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in dogs. The lack of stability data was noted as a minor deficiency. However, this is not expected to impact the results of the study.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test Material S-1563 (Momfluorothrin)
Description: White solid
Lot/Batch: 9CM0109G
Purity: 95.7%
CAS#: 609346-29-4
Stability: Cited to be "stable under storage conditions"

2. Vehicle None, S-1563 administered via gelatin capsules.

3. Test Animals
Species Dog
Strain Beagle
Age Approximately 6.5 – 7.0 months (males and females) at time of administration
Weight Approximately 7.0 - 10.6 kg (males) and 5.3 – 8.6 kg (females) at time of administration
Source Harlan Laboratories GmbH, Eustrup, Germany
Acclimation period From delivery under test conditions (3 weeks, 2.5 weeks for one animal).
Diet Pelleted standard Kliba 3353 dog maintenance diet (Provimi Kliba AG, Switzerland).
Water Tap water *ad libitum*.
Housing Group housing in pairs/group/sex. The animals were housed individually during dosing and feeding periods or at the discretion of the study director to facilitate recording of clinical signs and/or for performance of special investigations.
Environmental conditions
Temperature Room temperature: 20 - 23 °C
Humidity 30 - 70%
Air change 10 - 15 air changes per hour
Photoperiod 12-hour light/dark cycle

B. STUDY DESIGN:

1. In life dates: 15 December 2009 – 27 April2010

2. Animal assignment: Animals were assigned by weight stratification using a computer generated random algorithm to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Dose to animal (mg/kg/day)	# Male	# Female
Control	0	6	6
Low	60	4	4

Test group	Dose to animal (mg/kg/day)	# Male	# Female
Mid	200	4	4
High	600	6	6

3. **Dose selection rationale:** The dose levels were selected based on the results from a 2-week oral toxicity study where administration of up to 1,000 mg/kg/day resulted in salivation, tremors, and death. Administration of 500 mg/kg/day resulted in salivation, vomiting, and reduced body weights. Therefore, 600 mg/kg/day was chosen as the high-dose.

4. **Dosage preparation and analysis:** Appropriate amount of test item was weighed directly into a gelatin capsule and stored at 2-8 ºC. During the study, capsules at all dose levels were analyzed on day 1, at week 6, and at week 13 for stability and concentration.

Results:

Homogeneity analysis: N/A

Stability analysis: Reported as two weeks in refrigerator. Concentration analysis showed stability of two weeks.

Concentration analysis (% Nominal): 91.7 to 101.7%

5. **Statistics:** The following statistical methods were used to analyze body weight, clinical laboratory parameters, organ weights and pathology. All means are presented with standard deviations. All analyses are two-tailed for significance levels of 5% and 1%. Food consumption was not statistically analyzed. The Dunnett-test (many to one t-test) based on a pooled variance estimate was applied for the comparison of the treated groups and the control groups for each sex. The Steel-test (many-one rank test) was applied instead of the Dunnett-test when the data cannot be assumed to follow a normal distribution. Macropathology and histopathology data were analyzed using Fisher's Exact test (one tailed).

C. METHODS:

1. **Observations:**

   1a. Cageside observations: Animals were inspected twice daily for signs of toxicity and mortality.

   1b. Clinical examinations: Observations were performed before and approximately 1, 3 and 6 hours after application during the treatment period. A description of any abnormality was recorded.

2. **Body weight:** Animals were weighed at least twice weekly during pretest, twice weekly in the first four weeks of treatment and weekly thereafter including before necropsy and during recovery.

3. **Food consumption:** Food consumption was recorded daily from commencement of the

pretest period.

4. **Ophthalmoscopic examination:** Eyes were examined during pretreatment, at week 13 and week 19.

5. **Hematology and clinical chemistry:** Blood was collected during the test at weeks 4, 8 and 13 and in weeks 3 and 6 of recovery period from all animals. Blood was drawn from the jugular vein, early in the day, following overnight fasting. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
X	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

b. Clinical chemistry:

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus*	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
X	**ENZYMES** (more than 2 hepatic enzymes eg,*)	X	Total bilirubin*
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine amino-transferase (also SGPT)*		
X	Aspartate amino-transferase (also SGOT)*		
	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for subchronic non-rodent studies based on Guideline 870.3150

6. Urinalysis: Urine was collected during pretest, during the test at weeks 4/5, 8/9, 13/14 and in weeks 3 and 6 of recovery period from all animals. Urine was collected during overnight fasting; additional urine samples were collected on each occasion from each animal by catheterization.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity / osmolality*	X	Bilirubin
X	pH*	x	Blood / blood cells*
	Sediment (microscopic)	X	Nitrate
X	Protein*	X	Urobilinogen

* Recommended for subchronic non-rodent studies based on Guideline 870.3150

7. Sacrifice and pathology: All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Animals were anaesthetized by intravenous injection of sodium thiopentone and killed by exsanguination. Organs were collected and preserved in 4% neutral buffered formaldehyde. The (XX) organs, in addition, were weighed. Organs and tissues from all animals of all groups were further processed by embedding in paraffin, cutting at a nominal thickness of 2-4 micrometers, stained with hematoxylin & eosin (H&E) and examined by light microscope. Samples of liver and kidney were prepared for transmission electron microscopy. The liver and kidneys from the first two surviving animals from all groups after 13 weeks treatment were removed immediately at necropsy and weighed. Thereafter, a part of the liver and kidney (including medulla and cortex) was cut into small pieces (approximately 2mm x 2mm x 2mm) and immediately immersion fixed in modified Karnovsky fixative, 4% paraformaldehyde, 5% glutaraldehyde in 0.1 M sodium phosphate buffer (at pH 7.4), for approximately 1 to 3 days.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue	X	Aorta thoracic*	XX	Brain*+
XX	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus*+	X	**GLANDULAR**
X	Ileum*			XX	Adrenal gland*+
X	Cecum*	X	**UROGENITAL**	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	XX	Parathyroid*+
X	Rectum*	X	Urinary bladder*	XX	Thyroid*+
XX	Liver*+	XX	Testes*+	X	**OTHER**
XX	Gall bladder*+	XX	Epididymides*+	X	Bone (sternum and/or femur)
XX	Pancreas*	XX	Prostate*	X	Skeletal muscle
X	**RESPIRATORY**	XX	Ovaries*+	X	Skin*
X	Trachea*	XX	Uterus*+	X	All gross lesions and masses*
XX	Lung*	X	Mammary gland*		
X	Nose*				
X	Pharynx*				
X	Larynx*				

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150
+ Organ weight required for non-rodent studies.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** Higher incidences of watery, mucus or discolored feces and vomiting of mucus or feed were recorded in both sexes of the 600 mg/kg/day group. However, these signs were absent in the 6-week recovery animals. Increased salivation occurred in both sexes at 200 and 600 mg/kg/day during the first two weeks of treatment. However, this finding was transient and also recorded in three control males and considered a secondary effect possibly caused by the minimally irritating potential of the test item. Therefore, it is considered not to be of toxicological significance. All other effects recorded during clinical observations were not considered to be treatment-related.

2. **Mortality:** All animals survived until scheduled necropsy. No mortality was recorded.

B. BODY WEIGHT AND WEIGHT GAIN: There was no significant difference in bodyweight at any time during the study. Any initial mean body weight losses were regained by the end of the treatment period. These alterations were considered not to be toxicologically significant.

TABLE 2. Average body weights and during 90 days of treatment [a]

Dose rate (mg/kg/day)	Body weights (kg±SD)				
	Day -7	Day 1	Day 57	Day 92	Day 43 of recovery
Male					
0	8.9 ± 1.1	8.9 ± 1.1	9.5 ± 1.4	9.7 ± 1.7	9.3 ± 1.2
50	8.3 ± 1.0	8.4 ± 1.0	9.3 ± 1.0	9.3 ± 0.9	-
200	8.4 ± 1.3	8.4 ± 1.0	8.6 ± 1.3	8.7 ± 1.3	-
600	8.6 ± 0.9	8.6 ± 0.9	8.7 ± 0.9	9.5 ± 1.0	8.6 ± 0.6
Female					
0	6.5 ± 1.1	6.5 ± 1.1	7.3 ± 1.0	7.5 ± 0.8	8.4 ± 1.2
50	6.9 ± 1.0	7.0 ± 1.1	7.8 ± 1.4	8.2 ± 1.5	-
200	6.8 ± 1.4	6.8 ± 1.4	7.1 ± 1.0	7.5 ± 0.7	-
600	6.8 ± 0.5	6.8 ± 0.5	7.1 ± 0.6	7.7 ± 0.3	8.3 ± 1.0

[a] Data obtained from pages 53-58 in MRID 49020008.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** No significant changes in food consumption were reported.

2. **Compound consumption:** Administered in capsules.

3. **Food efficiency: N/A**

D. OPHTHALMOSCOPIC EXAMINATION: There were no ophthalmoscopic changes which were considered to be related to treatment.

E. BLOOD ANALYSES:

1. **Hematology:** No treatment-related effects were identified for either sex at any dose level.

2. **Clinical chemistry:** Sporadic increases in cholesterol and triglycerides were observed at 600 mg/kg throughout the study. However, these increases did not reach statistical significance at week 13 and were not observed following the recovery period. Therefore, they were not considered to be toxicologically relevant.

F. URINALYSIS: No treatment-related effects were identified for either sex at any dose level.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** Slight (not statistically significant) increases in absolute (11%/14% in ♂/♀) and relative (11% in both sexes) liver weights were observed at 600 mg/kg/day. These weights were comparable to those of controls following the 6-week recovery period. No

further treatment-related effects were identified.

2. **Gross pathology:** No treatment-related macroscopic findings were identified in either sex at any dose level.

3. **Microscopic pathology:** Minimal to slight centrilobular hepatocellular hypertrophy was recorded in four male and two female high dose animals (600 mg/kg/day). This finding was not observed after the recovery period.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The study author concluded that a dose of 600 mg/kg/day in males and females resulted in slight changes in the liver such as blood liver parameters (i.e. cholesterol and triglyceride), slightly increased mean liver weights and microscopic effects in the liver (centrilobular hepatocellular hypertrophy) indicative of metabolic changes due to effects of the test item and considered adverse effects. Furthermore, a high incidence of vomiting was recorded. These changes were completely reversible. Based on the results in this study, the no-observed-adverse-effect-level (NOAEL) is considered to be 200 mg/kg/day in males and females.

B. REVIEWER COMMENTS: Clinical signs including: higher incidences of watery, mucus or discolored feces and vomiting of mucus or feed and slight evidence of hepatotoxicity (increased liver weights, increased cholesterol and triglyceride levels, and histopathological findings) were observed in both sexes at 600 mg/kg.

The systemic toxicity LOAEL for this study is 600 mg/kg/day based on clinical signs (watery, mucus or discolored feces and vomiting of mucus or feed) and slight evidence of hepatotoxicity including non-significant, but dose-related, increases in liver weights, and slight to minimal hepatocellular hypertrophy. The systemic toxicity NOAEL is 200 mg/kg/day.

C. STUDY DEFICIENCIES: Minor deficiency: Stability data not provided.